Exchange

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Introduction

The processes of water exchange between tissue compartments may have a profound effect on the physical interpretation of MRI data. Water exchange is mediated by semi-permeable cell membranes and vascular walls. Water molecules in tissues exhibit random Brownian motion, therefore during the time-frame of the MR experiment most of them can be found in the vicinity of thecell membrane or vascular wall. Although for most permeable cell membrane (red blood cell) only one in 10^4 of these molecules eventually crosses the cell membrane, in 10-100ms (typical timeframe for MR experiment), most of the water molecules will experience cellular walls many times and therefore most of them will migrate from one tissue compartment to the other. Exchange process in tissue is difficult to assess, therefore it is common to assume in MRI models that the exchange processes are fast (perfusion models) or to entirely neglect them (diffusion data interpretation). In this paper the exchange process is presented and its effects on tissue relaxation and diffusion data interpretation are discussed.

Cell Membrane Permeability

The exchange process between liquid tissue compartments (intra-, extracellular, plasma and blood) are thought to be mediated by the process of water molecules diffusion through the semi-permeable membranes (1). It is common to express cell membrane permeability, P, in the terms of the pseudo-first order exchange rate k_{IE}:

$$k_{IE} = P\frac{S}{V} \qquad [1]$$

where S/V is a surface-to-volume ratio of the cell. The cell membrane permeability, P, depends on the type of cell membrane and the mobility of water inside the cell. The literature data concerning cell membrane permeability for water are very limited and P is only accurately known for RBC (2.5–3.0) x 10^{-3} cm s^{-1} (1) . For other types of cells, P is estimated to be lower than that of RBC, but in most cases larger than 0.5 x10^{-3} cm s^{-1}. *In vitro* MRI experiments in bovine optic nerve estimated axonal and glial permeability at (0.9 ± 0.2) and (1.7 ± 0.3) x10^{-3} cm s^{-1}, respectively (2).

The inverse of k_{IE} defines the average residence time, τ, of the water molecule inside the cell. It is therefore evident that the exchange rate constant (thus τ) depends not only on P, but also on cellular size and cell shape. It is apparent that water inside cells with small diameter has a relatively short τ . In contrast, τ is large for large cells. This is to be expected, since for the larger cellular size, it would take longer for an average water molecule to reach the cell membrane and eventually cross it. τ has been estimated previously to range from approximately 12 ms for RBC (3), to 600 ms for neuronal cells (4).

Tissue Compartments and Exchange

Due to structural heterogeneity contrast mechanisms in tissue are often complex. It is common to approximate tissue microstructure using multi-compartmental tissue models (Fig.1).

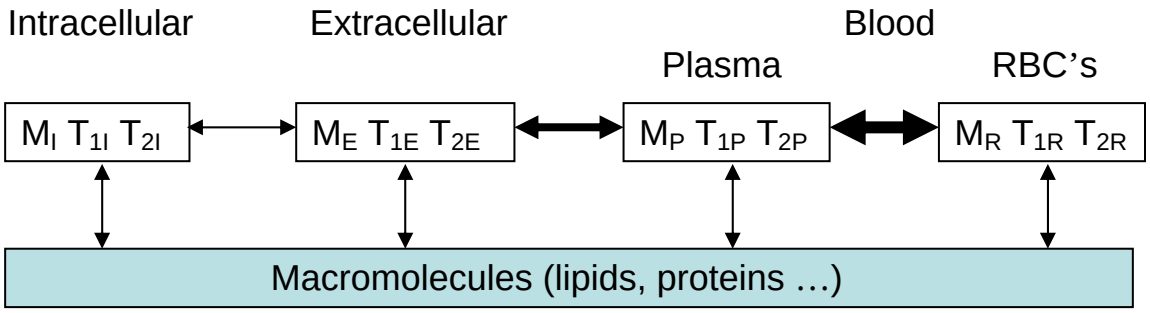

Figure 1. Compartmental model of tissue. Each compartment has its own magnetization, M and intrinsic longitudinal, T_1 and transverse, T_2 relaxation times. The spins are allowed for exchange (arrows) between tissue compartments. The macromolecular pool is not "visible" in a standard MRI experiment , due to its extremely short T_2 relaxation (in order of μs (5)). However, it may significantly influence MR parameters of "visible" liquid protons in intra, extra and blood compartments.

Since the physical environment of water in different tissue compartments is vastly different, there is no reason to believe that the intrinsic relaxation times in tissue compartments are similar. For example T_2 relaxation of red blood cell (RBC) is on the order of 130 ms (6), whereas T_2 of plasma is approximately 700 ms. Therefore, one may expect multi-exponential behavior of T_2 or T_1 relaxation tissue. In particular, T_2 relaxation could be expressed as:

$$M(t) = \sum_i M_i \exp(-t/T_{2i}) \quad [2]$$

where i denotes various tissue compartments. The physical interpretation of the relaxation decay is however, much more complex than eq. [2] would indicate. This is because of the exchange of protons between various tissue compartments. On the typical scale of the MR experiment (~hundreds of ms) the water proton can migrate from one tissue compartment to the other or exchange its spins with immobile protons associated with macromolecules. The processes of inter-compartmental exchange have been shown to have a profound effect on MR measures of tissue such as T_1 and T_2 and diffusion. The exchange process can be easily incorporated into the standard Bloch equations describing the magnetization behavior. For example for the simplest case of the two-compartmental system consisting of intra and extracellular water the magnetization of each of the pools can be described as:

$$\frac{dM_I}{dt} = -R_I M_I - k_{IE} M_I + k_{EI} M_E \quad [3]$$
$$\frac{dM_E}{dt} = -R_E M_E + k_{IE} M_I - k_{EI} M_E$$

where $M_{I,E}$ denote the magnetization in intra (I) and extracellular (E) space, $R_{I,E}$ the rates of decay (1/T2) and k_{EI} exchange ratio from extracellular to intracellular space, which has to satisfy the boundary condition, in order to preserve the spin densities in intra- and extracellular space:

$$M_I(0)k_{IE} = M_E(0)k_{EI} \quad [4]$$

$M_{I,E}(0)$ denote equilibrium magnetization in each of the pools. Eqs. 3-4 can be readily solved, showing that the total magnetization of two-compartmental system (M_I+M_E) decays bi-exponentially with two well distinguished rates as is

illustrated in Fig.2. In the absence of exchange (k_{IE}=0) the total magnetization is characterized by two relaxation rates that are equal to the intrinsic decay rates $R_{I,E}$ of intra and extracellular pools. The relative amplitudes of those decay rates are also equal to the populations of intra and extracellular (Fig.2a). However, when the exchange is present both the decay rates and their relative amplitudes are <u>not</u> equal to the intrinsic ones as shown in Fig.2b. Finally, when the exchange rate is very fast the system decays mono-exponentially with the rate that is equal to the weighted average of intrinsic rates $R=(M_I*R_I+ME*R_e)/(M_I+M_E)$. This scenario is often described in terms of three exchange regimes (7,8):

a) Slow ($R_{I,E}>>k_{IE}$)
b) Intermediate ($R_{I,E}\sim k_{IE}$)
c) Fast ($R_{I,E}<<k_{IE}$)

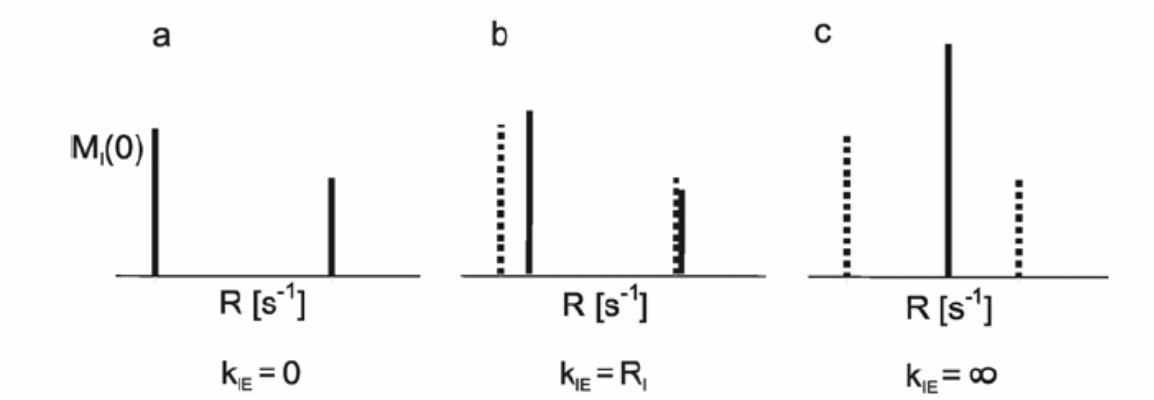

Figure 2. The relaxation components of two-pool model system in the case of negligible (a), intermediate (b) and fast exchange (c). The dotted lines represent intrinsic relaxation rates of two pools. Note that both the amplitudes and positions of relaxation rates, in the presence of exchange do not correspond to the intrinsic ones. In the case of the fast exchange regime the system decays with single relaxation rate constant that is weighted average of intra and extracellular components.

Perfusion:

Dynamic Contrast Enhancement (DCE) MRI is based on the indirect detection of contrast agent (CA) by measuring MR characteristics of tissue during bolus injection of CA. Most DCE MRI models are based on mathematical formalism developed by Tofts (9). This model is based on three following assumptions:

1. the water in different tissue compartments is in a fast exchange regime (total "mixing" of water),
2. the CA is uniformly distributed in a tissue compartment,
3. the CA effect on water characteristics in tissue is similar to that of saline.

As a consequence of these assumptions the CA concentration in tissue can be calculated from the MR signal using the following formula:

$$\frac{1}{T_1} = \frac{1}{T_1^0} + r_1[Gd] \qquad [5]$$

where T_1, T_1^0 denote the T_1 relaxation times in the presence and absence of CA, respectively; [Gd] is a concentration of CA in tissue compartment and r_1 is a relaxivity of CA in saline.

It has to be noted that eq. [5] is valid only in the case of fast exchange regime. However, high concentration of CA cause the T_1 relaxation to deviate from mono-exponential behaviour. Thus commonly accepted models usually lead to systematic overestimation of the perfusion transfer constant, K^{trans}, and potentially large overestimation of the blood plasma volume fraction (10). In fact, even in the blood pool alone, T_1 relaxation may not be mono-exponential for high concentration (2mM) of intravascular contrast agent (i.e. Gd-17) with high T_1 relaxivity.
In recent years, heterogenous DCE MRI models, in which CAs are not assumed to be uniformly distributed with each tissue compartment (11) (10) and water exchange process are taken into account (12) have been proposed. They significantly reduce systematic errors in perfusion parameters. This reduction however comes at the cost of an increased number of model parameters necessary to perform data analysis.

Diffusion:

The effects of compartmental exchange on the diffusion signal can be easily incorporated into the diffusion models using the modified Bloch equations proposed by Karger (13) and first implemented by Andrasko in blood (1), and recently tested for white matter (14) and red blood ghost cells (15). It has to be noted, however, that the Bloch equations with exchange in the presence of diffusion are substantially different in their physical interpretation than those for T_1 or T_2 relaxation. This difference is due to the fact that the "decay rate constant" for diffusion, R_{diff}, is defined as:

$$R_{diff} = q^2 ADC \qquad [6]$$

Where diffusion factor $q = \gamma g \delta$ (γ gyromagnetic ratio, g and δ are diffusion gradient amplitude and duration respectively). ADC denotes the apparent diffusion coefficient in intra or extracellular compartments. Therefore, R_{diff} depends on the experimental parameters (q) and ADC. In contrast to the longitudinal ($1/T_1$) or transverse ($1/T_2$) rate constants, R_{diff} is not a constant.
In consequence, the "slow", "intermediate", and "fast" exchange regimes depend on experimental conditions. In the constant diffusion time experiment (cd) when q varies (usually by increasing gradient strength, g), R_{diff} increases; whereas in the constant gradient experiment (cg) where diffusion time, Δ, is varied, R_{diff} remains constant in extracellular compartments and decreases with Δ in intracellular ones (due to changes in intracellular ADC). Consequently, these two types (cd and cg) of experiments may yield different diffusion curves, which has been observed by Norris and Niendorf (16). Figure 3 shows the values of intra- and extracellular R_{diff} as a function of diffusion parameter q:

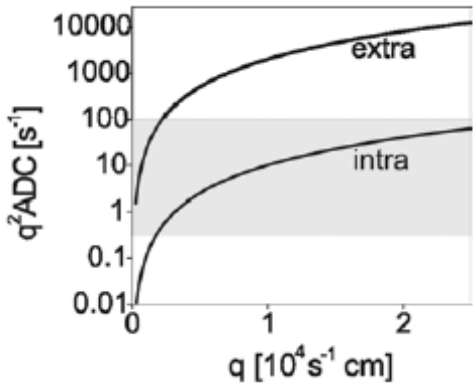

Figure 3. Diffusion rate decay, Rdiff, as a function of q for intra and extracellular ADCs. The shaded region represents a typical range of exchange between intra- and extracellular compartments. For the small q values, R_{diff} is slower than k_{IE}, representing the "fast exchange" regime, where the total mixing of the two pools is observed. As q increases, R_{diff} becomes comparable to k_{IE}, allowing for separation of the pools (intermediate exchange regime)

For small values of q (and therefore small b in the case of the "cd" experiment), $R_{diff} < k_{IE}$ and therefore fast exchange regime is anticipated; if q increases, R_{diff} is comparable with k_{IE} and intermediate regime occurs. Consequently, the signal decay due to diffusion in a system consisting of two different exchanging compartments changes drastically. This is illustrated in Fig. 4. which shows the normalized diffusion signal decay S(b)/S(0) for a model system of white matter as a function of diffusion parameter, b, for the range of the exchange rates, k_{IE}, and two diffusion times Δ, 10 and 50 ms. The PGSE signal as measured in the direction perpendicular to axons is shown.

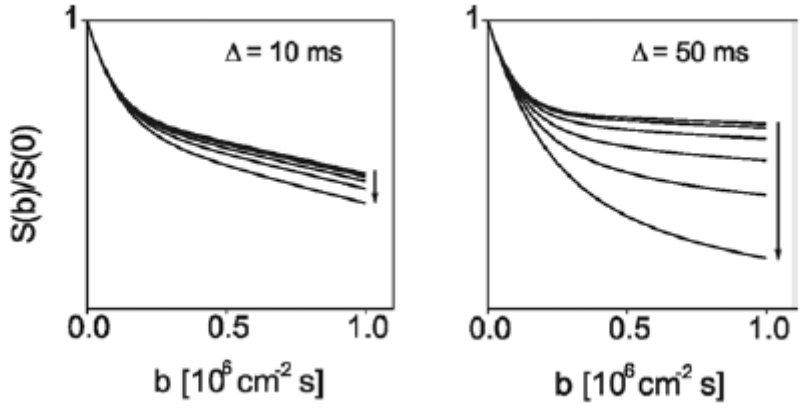

Figure 4. The diffusion curves for the two-compartmental system for two diffusion times and the range of permeabilites. The arrows indicate increasing k_{IE} ranging from (0, 1, 2, 5, 10, and 20 s–1) or decreasing intracellular residence time, τ (∞, 1000, 500, 200, 100, and 50 ms).

Because of the "fast" exchange regime for the small q values, increased exchange *does not change* the initial slope of the diffusion curve, which is equal to the weighted average of the apparent diffusion coefficients inside and outside cells:

$$ADC = V_I ADC_I + V_E ADC_E \qquad [7]$$

This also means that the diffusion experiments for the small b values (as in clinical MRI) are insensitive to changes in cell membrane permeability. However, inter-compartmental exchange can markedly change diffusion curve characteristics for high b values. As expected, increased exchange results in a significant signal decrease at high b values. For short diffusion times, Δ, the effects of exchange are small because during this time few molecules will experience the cell membranes. In the case presented, the average residence time of water inside the axon (approximately 33 ms (14)) is much longer than Δ (10 ms). However, for longer diffusion times (comparable to the average residence time inside the cell, τ—Fig. 4b) the effect of inter-compartmental exchange cannot be neglected. When the PGSE signal decay is non-mono-exponential, it is often fitted to a phenomenological, bi-exponential model of diffusion. This approach, however, may lead to an overestimation of intracellular, and underestimation of extracellular ADCs and cellular volume fraction (2). In the case of gray matter where the neuron size varies (5 to 200 μm) the influence of exchange varies as well – it influences small neurons, where residence time is short (due to small surface to volume ratio) and is negligible for large axons where average residence time is in order of hundreds of ms.

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